What is the clinical presentation of patients with confirmed COVID-19?

(See Centers for Disease Control and Prevention [CDC] COVID-19: Clinical Care, 06/30/2020; CDC FAQ for Healthcare Professionals, 06/04/2020; and National Institutes of Health [NIH] COVID-19 Treatment Guidelines, 06/16/2020)

- Incubation period: median four to five days from exposure to symptoms onset (extends to 14 days).

**Signs and symptoms:**
- Fever (83% to 99%)
- Cough (59% to 82%)
- Fatigue (44% to 70%)
- Anorexia (40% to 84%)
- Shortness of breath (31% to 40%)
- Sputum production (28% to 33%)
- Myalgias or muscle aches (11% to 35%)
- Loss of smell or taste
- Chills or repeated shaking with chills

**Less common symptoms (<10%):**
- Headache
- Confusion
- Rhinorrhea
- Sore throat
- Hemoptysis
- Gastrointestinal symptoms: vomiting, diarrhea, nausea

**Asymptomatic and pre-symptomatic infection and transmission:**
- Several studies have documented SARS-CoV-2 infection in patients who never develop symptoms (asymptomatic) and in patients not yet symptomatic (pre-symptomatic).
- Since asymptomatic persons are not routinely tested, the prevalence of asymptomatic infection and detection of pre-symptomatic infection are not well understood.
- Some data suggest that pre-symptomatic infection tended to be detected in younger individuals and was less likely to be associated with viral pneumonia.
- Epidemiologic studies have documented SARS-CoV-2 transmission during the pre-symptomatic incubation period, and asymptomatic transmission has been suggested in other reports. Virologic studies also have detected SARS-CoV-2 with reverse transcription polymerase chain reaction (RT-PCR) low-cycle thresholds, indicating larger quantities of viral RNA, and cultured viable virus among persons with asymptomatic and pre-symptomatic SARS-CoV-2 infection.
The exact degree of SARS-CoV-2 viral RNA shedding that confers risk of transmission is not yet clear. Risk of transmission is thought to be greatest when patients are symptomatic, since viral RNA shedding is greatest at the time of symptom onset and declines over the course of several days to weeks.

- **Signs and symptoms in children:** For more information on the clinical presentation and course among children, see [Information for Pediatric Healthcare Providers](#).

**When is someone with COVID-19 infectious, and which body fluids can spread infection?**

*(See CDC [FAQ for Healthcare Professionals](#), 07/23/2020, and CDC [Clinical Care](#), 06/30/2020)*

According to CDC, the onset and duration of viral shedding and period of infectiousness for COVID-19 are not yet known with certainty. Based on current evidence, scientists believe persons with mild to moderate COVID-19 may shed replication-competent SARS-CoV-2 for up to 10 days following symptom onset, while a small fraction of persons with severe COVID-19, including immunocompromised persons, may shed replication-competent virus for up to 20 days. It is possible that SARS-CoV-2 RNA may be detectable in the upper or lower respiratory tract for weeks after illness onset. However, detection of viral RNA does not necessarily mean infectious virus is present.

Increasing numbers of epidemiologic studies have documented SARS-CoV-2 transmission during the pre-symptomatic incubation period. Virologic studies using RT-PCR detection have reported tests with low-cycle thresholds, indicating larger quantities of viral RNA and viable virus have been cultured from persons with asymptomatic and pre-symptomatic SARS-CoV-2 infection. The relationship between SARS-CoV-2 viral RNA shedding and transmission risk is not yet clear. The proportion of SARS-CoV-2 transmission due to asymptomatic or pre-symptomatic infection compared with symptomatic infection is unclear. Based on existing literature, the incubation period (the time from exposure to development of symptoms) of SARS-CoV-2 and other coronaviruses (e.g. MERS-CoV, SARS-CoV) ranges from 2-14 days.

SARS-CoV-2 RNA has been detected in upper and lower respiratory tract specimens, and SARS-CoV-2 virus has been isolated from upper respiratory tract specimens and bronchoalveolar lavage fluid. SARS-CoV-2 RNA has been detected in blood and stool specimens, and SARS-CoV-2 virus has been isolated in cell culture from the stool of some patients. The duration of SARS-CoV-2 RNA detection in upper and lower respiratory tract specimens and in extrapulmonary specimens is not yet known but may be several weeks or longer. While viable infectious SARS-CoV has been isolated from respiratory, blood, urine, and stool specimens, it is not yet known whether other non-respiratory body fluids from an infected person including vomit, breast milk, or semen can contain viable infectious SARS-CoV-2.

**Can individuals who recover from COVID-19 be reinfected with SARS-CoV-2?**

*(See CDC [FAQ for Healthcare Professionals](#), 06/04/2020; CDC [COVID-19: Clinical Care](#), 06/30/2020)*

The immune response, including duration of immunity, to SARS-CoV-2 infection is not yet understood. There are no data concerning the possibility of re-infection with SARS-CoV-2 after recovery from COVID-19. Viral RNA shedding declines with resolution of symptoms and may continue for days to weeks. The detection of RNA during convalescence does not necessarily indicate the presence of viable infectious virus. Clinical recovery has been correlated with the detection of IgM and IgG antibodies, which signal the development of immunity. However, definitive data are lacking, and it remains uncertain whether individuals with antibodies are protected against reinfection with SARS-CoV-2, and if so, what concentration of antibodies is needed to confer protection.
What are the risk factors for COVID-19?
(See CDC COVID-19: Clinical Care, 06/30/2020; CDC FAQ for Healthcare Professionals, 06/04/2020; and CDC COVID-19 High-Risk Conditions, 05/14/2020)

- Currently, those at greatest risk of infection are persons who have had prolonged, unprotected close contact with a patient with symptomatic, confirmed COVID-19 and those who live in or have recently been to areas with sustained transmission.

- Age is a strong risk factor for severe illness, complications, and death. Based on currently available information and clinical expertise, older adults and people of any age who have serious underlying medical conditions might be at higher risk for severe illness from COVID-19. For more information, see Assessing Risk Factors for Severe COVID-19 Illness (CDC, 04/23/2020).

- Based upon available information to date, those at high risk for severe illness from COVID-19 are:
  - People of all ages with underlying medical conditions, particularly if not well controlled, including:
    - Cancer
    - COPD
    - Serious heart conditions
    - Chronic kidney disease
    - Obesity (BMI ≥ 30)
    - Type 2 diabetes
    - Sickle cell disease
    - Immunocompromised state from solid organ transplant

- Based on available information to date, those who might be at an increased risk for severe illness from COVID-19 are those at any age with the following underlying conditions:
  - Asthma
  - Cerebrovascular disease
  - Cystic fibrosis
  - Hypertension or high blood pressure
  - Immunocompromised state from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
  - Neurologic conditions
  - Liver disease
  - Pregnancy
  - Pulmonary fibrosis
  - Smoking
  - Hemoglobin disorders
  - Type 1 diabetes

What is the clinical course of COVID-19?
(See CDC COVID-19: Clinical Care, 06/30/2020)

- CDC states that current research shows illness severity ranging from mild to critical:
  - Mild to moderate (mild symptoms up to mild pneumonia): 81%
  - Severe (dyspnea, hypoxia, or >50% lung involvement on imaging): 14%
  - Critical (respiratory failure, shock, or multiorgan system dysfunction): 5%

- Among patients who developed severe disease:
  - The median time to dyspnea ranged from five to eight days;
The median time to acute respiratory distress syndrome (ARDS) ranged from eight to 12 days; and
The median time to ICU admission ranged from 10 to 12 days.

Clinicians should be aware of the potential for some patients to rapidly deteriorate one week after illness onset.

Among all hospitalized patients, a range of 26% to 32% of patients were admitted to the ICU, and mortality among patients admitted to the ICU ranges from 39% to 72%, depending on the study.

The median length of hospitalization among survivors was 10 to 13 days.

What is the recommended diagnostic testing for COVID-19?
(See CDC Overview of Testing for SARS-CoV-2, 06/13/2020, and CDC COVID-19: Clinical Care, 06/30/2020)

Infection with both SARS-CoV-2 and with other respiratory viruses has been reported, and detection of another respiratory pathogen does not rule out COVID-19.

Authorized assays for viral testing include those that detect SARS-CoV-2 nucleic acid or antigen. **Viral (nucleic acid or antigen) tests** check samples from the respiratory system (such as nasal swabs) and identify if an infection with SARS-CoV-2, the virus that causes COVID-19, is present. Viral tests are recommended to diagnose acute infection. Some tests are point-of-care tests, meaning results may be available at the testing site in less than an hour. Other tests must be sent to a laboratory to analyze, a process that may take 1-2 days once received by the lab. Testing the same individual more than once in a 24-hour period is not recommended. For more information on testing, please refer to TMA's COVID-19 Testing Information Frequently Asked Questions (FAQs).

For more information on diagnostic testing for COVID-19 see the Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens and Biosafety FAQs for handling and processing specimens from possible cases.

What is the optimal imaging technique for people with COVID-19?
(See NIH COVID-19 Treatment Guidelines, 06/16/2020)

According to NIH:

- The optimal pulmonary imaging technique for people with COVID-19 is yet to be defined.
- Initial evaluation may include chest x-ray, ultrasound, or if indicated, computerized tomography (CT).
- Electrocardiogram should be performed if indicated.
- Laboratory testing includes a complete blood count (CBC) with differential and a metabolic profile, including liver and renal function tests.
- Measurements of inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin, while not part of standard care, may have prognostic value.

What are the most common laboratory and radiographic findings of COVID-19?
(See CDC COVID-19: Clinical Care, 06/30/2020)

- Lympopenia (83%)
- The following may be associated with greater illness severity:
  - Neutrophilia
  - Elevated serum alanine aminotransferase and aspartate aminotransferase levels
  - Elevated lactate dehydrogenase
  - High CRP
  - High ferritin levels
• Elevated D-dimer and lymphopenia have been associated with mortality.
• Procalcitonin is typically normal on admission but may increase among those admitted to the ICU.
• Patients with critical illness had high plasma levels of inflammatory makers, suggesting potential immune dysregulation.
• Chest CT imaging commonly demonstrates bilateral, peripheral ground-glass opacities. According to the American College of Radiology (03/22/2020):
  ◦ CT should not be used to screen for or as a first-line test to diagnose COVID-19.
  ◦ CT should be used sparingly and reserved for hospitalized, symptomatic patients with specific clinical indications for CT.

What is the recommended clinical management and treatment for COVID-19 in outpatient and inpatient settings?

(See CDC COVID-19: Clinical Care, 06/30/2020, and NIH COVID-19 Treatment Guidelines, 06/16/2020)

• **There is currently no specific FDA-approved treatment for COVID-19.**

• For information on the recommended clinical management and treatment for COVID-19 from NIH, see the complete NIH COVID-19 Treatment Guidelines.

• According to CDC, the decision to monitor a patient in the inpatient or outpatient setting should be made on a case-by-case basis, taking into account the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and the ability to self-isolate. For more information, see CDC Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) (06/30/2020).

• Patients with **mild** clinical presentation (absence of viral pneumonia and hypoxia) may not initially require hospitalization, and many patients will be able to manage their illness at home.

• Patients with risk factors for severe illness should be monitored closely given the possible risk of progression to severe illness in the second week after symptom onset. Some patients with COVID-19 will have severe disease requiring hospitalization for management.

**Outpatient Management** (See CDC Interim Guidance for Implementing Home Care of People Not Requiring Hospitalization for COVID-19, 06/16/2020)

• Ensure appropriate infection control. For information regarding infection prevention and control recommendations, please see TMA’s COVID-19 Infection Prevention and Control for Outpatient Clinics Frequently Asked Questions (FAQs).

• CDC provides guidance for patients evaluated in an outpatient setting who do not require hospitalization (i.e., patients who are medically stable and can receive care at home) or patients who are discharged home following a hospitalization with confirmed COVID-19 infection, to undergo home care.

• A physician should provide CDC’s Interim Guidance for Preventing Coronavirus Disease 2019 (COVID-19) from Spreading to Others in Homes and Communities to the patient, caregiver, and household members.

**Inpatient Management**

• Inpatient management of COVID-19 revolves around the supportive management of the most common complications of severe COVID-19:
  ◦ Pneumonia
  ◦ Hypoxemic respiratory failure/ARDS
  ◦ Sepsis and septic shock
- Cardiomyopathy and arrhythmia
- Acute kidney injury
- Complications from prolonged hospitalization, including:
  - Secondary nosocomial infections
  - Thromboembolism
  - Gastrointestinal bleeding
  - Critical illness polyneuropathy/myopathy
- Some patients with COVID-19 may develop signs of a hypercoagulable state and be at increased risk for venous and arterial thrombosis of large and small vessels. More information on hypercoagulability and COVID-19 is available from the American Society of Hematology.

**Oxygenation and ventilation:**
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, NIH recommends considering a trial of awake prone positioning to improve oxygenation (CIII).
- NIH recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation (AIII).

**What are the investigational therapeutics for COVID-19?**

*(See CDC Therapeutic Options for Patients with COVID-19, 04/25/2020, and NIH COVID-19 Treatment Guidelines, 07/24/2020)*

- There are no drugs or other therapeutics approved by FDA to prevent or treat COVID-19. Current clinical management involves infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated.
- NIH has published interim guidelines for the medical management of COVID-19 prepared by the COVID-19 Treatment Guidelines Panel. These guidelines contain information about investigational therapeutics and will be updated as new information emerges and drugs and other therapeutic interventions are approved for use by FDA.
- Persons seeking information about registered clinical trials for COVID-19 in the United States can search for such information here: ClinicalTrials.gov.
- Please see the Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection (04/21/2020) for a list of treatment recommendations and narrative summaries of other treatments undergoing evaluations.
- Current investigational agents, drugs, and therapies of note are described below.
  - **Remdesivir** is an investigational intravenous drug with broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related betacoronaviruses.

Because remdesivir supplies are limited, NIH recommends remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (B). NIH recommends the investigational antiviral agent remdesivir for treatment of COVID-19 in hospitalized patients with SpO2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen for five days or until hospital discharge, whichever comes first. There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical
improvement after five days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days.

- NIH cannot make a recommendation for or against remdesivir for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO). In a randomized clinical trial, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

- There are insufficient data for NIH to recommend for or against remdesivir for the treatment of patients with mild or moderate COVID-19.

- Hydroxychloroquine or chloroquine are oral prescription drugs that have been used for treatment of malaria and certain inflammatory conditions.

- NIH recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial. Given the risk of dysrhythmias, the Food and Drug Administration (FDA) cautions against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 outside of a hospital or clinical trial.

- NIH recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19.

- NIH recommends against the use of hydroxychloroquine plus azithromycin for the treatment of COVID-19, except in the context of a clinical trial.

- Convalescent plasma (See FDA Recommendations for Investigational COVID-19 Convalescent Plasma, 05/01/2020; Investigational COVID-19 Convalescent Plasma - Emergency INDs Frequently Asked Questions, 04/03/2020; and NIH COVID-19 Treatment Guidelines, 06/16/2020):

  - NIH states there are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19.
  
  - FDA has issued guidance for health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency.

- Dexamethasone is a synthetic corticosteroid medication used for suppressing the immune system and inflammation. University of Oxford's RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial found that dexamethasone reduced deaths by one-third in ventilated patients and by one fifth in other patients receiving oxygen only. There was no benefit among those patients who did not require respiratory support. The preliminary report has been published in the New England Journal of Medicine.

- Other drugs: Several other drugs (e.g., investigational antivirals; immunotherapeutic, host-directed therapies) are under investigation in clinical trials or are being considered for clinical trials of pre-exposure prophylaxis, post-exposure prophylaxis, or treatment of COVID-19 in the U.S. and worldwide. Information on registered clinical trials for COVID-19 in the U.S is available at ClinicalTrials.gov.

- NIH recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (AI) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (BI).

- NIH recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (AI).
The Milken Institute is currently tracking (06/18/2020) the development of treatments and vaccines for COVID-19, providing a document that contains an aggregation of publicly available information from validated sources.

In the absence of an approved vaccine, community mitigation measures and adherence to recommended infection prevention and control measures are the ways to reduce SARS-CoV-2 transmission among persons in the community and in health care facilities.

**What are the recommendations for pre- or post-exposure prophylaxis treatment?**

*(NIH COVID-19 Treatment Guidelines, 06/16/2020)*

- According to NIH, at present, no agent is known to be effective for preventing SARS-CoV-2 infection before an exposure (i.e., as PrEP) or after an exposure (i.e., as PEP).
- NIH does not recommend the use of any agents for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) against SARS-CoV-2 outside of the setting of a clinical trial.

**When can you advise the patient to discontinue transmission-based precautions or home isolation?**

*(See CDC Discontinuation of Transmission-Based Precautions and Disposition of Patients with COVID-19 in Healthcare Settings (Interim Guidance), 04/30/2020, and CDC Interim Guidance for Implementing Home Care of People Not Requiring Hospitalization for Coronavirus Disease 2019 (COVID-19), 06/16/2020)*

**Symptom-based strategy for patients with mild or moderate illness who are not severely immunocompromised:**

- At least 24 hours have passed since recovery – defined as resolution of fever without the use of fever-reducing medications and improvement in symptoms (e.g., cough, shortness of breath), and
- At least **10 days** have passed since symptoms first appeared.
- For patients who are not severely immunocompromised and asymptomatic throughout their infection, transmission-based precautions can be discontinued when at least 10 days have passed since the date of positive viral diagnostic test.

**Symptom-based strategy for patients with severe to critical illness or who are severely immunocompromised:**

- At least 24 hours have passed since recovery – defined as resolution of fever without use of fever-reducing medications and improvement in symptoms (e.g., cough, shortness of breath), and
- At least **20 days** have passed since symptoms first appeared.
- For patients who are severely immunocompromised and asymptomatic throughout their infection, transmission-based precautions can be discontinued when at least 20 days have passed since the date of positive viral diagnostic test.

**Test-based strategy for discontinuing transmission-based precautions.**

A test-based strategy is no longer recommended because, in the majority of cases, it results in prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA but are no longer infectious.

- In some instances, a test-based strategy could be considered for discontinuing transmission-based precautions earlier than if the symptom-based strategy were used. However, many individuals will have prolonged viral shedding, limiting the utility of this approach. A test-based strategy could also be considered for some patients (e.g., those who are severely immunocompromised) in consultation with local infectious diseases experts if concerns exist for the patient being infectious for more than 20 days.
• The criteria for the test-based strategy are:
  ◦ Patients who are symptomatic:
    · Resolution of fever without the use of fever-reducing medications,
    · Symptoms (e.g., cough, shortness of breath) have improved, and
    · Results are negative from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) tested using an FDA-authorized molecular viral assay to detect SARS-CoV-2 RNA.
  ◦ Patients who are not symptomatic: Results are negative from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) tested using an FDA-authorized molecular viral assay to detect SARS-CoV-2 RNA.

For health care personnel, see CDC Criteria for Return to Work for Healthcare Personnel with Suspected or Confirmed COVID-19 (Interim Guidance), 04/30/2020.

How is COVID-19 treatment paid for?
• Visit TMA’s Practice Help page for information on COVID-19 testing and treatment reimbursement, including:
  • Telemedicine;
  • Payers/Insurance; and
  • Billing and Coding
  ◦ AMA: Special coding advice during COVID-19 public health emergency.

For other information not addressed in this FAQ, please refer to the following resources:
- CDC Coronavirus COVID-19 website
- TMA COVID-19 Resource Center
- DSHS Coronavirus Disease (COVID-19) website
- CDC 24/7 COVID-19 Clinician Guidance Hotline at (770) 488-7100
- DSHS COVID-19 Call Center: 2-1-1 Option 6, Monday-Friday, 7 am-8 pm;
- DSHS email: coronavirus@dshs.texas.gov
- TMA Knowledge Center (800) 880-7955 or knowledge@texmed.org

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